June 14, 2002

VETERINARY SERVICES MEMORANDUM NO. 800.202

Subject: General Licensing Considerations: Efficacy Studies

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

These general licensing considerations provide guidance to licensees, permittees, and applicants concerning the submission of documents to support an application for a U.S. Veterinary Biological Product License or U.S. Veterinary Biological Product Permit for Distribution and Sale according to 9 CFR 102.5 and 104.5.

II. REPLACEMENT

This memorandum replaces Veterinary Services Memorandum No. 800.200 dated January 18, 2000.

III. BACKGROUND

General Licensing Considerations address basic principles that have general application in the licensing of products. This document addresses basic principles for conducting efficacy studies.

IV. GUIDELINES

The General Licensing Considerations: Efficacy Studies is appended to this memorandum.

/s/ W. Ron DeHaven

W. Ron DeHaven
Deputy Administrator
Veterinary Services

Enclosure

General Licensing Considerations: Efficacy Studies

1. Introduction
2. Materials
3. Methods
4. Criteria

1. Introduction

1.1 *Aim*. This document gives guidance for efficacy studies supporting the licensure of veterinary biological products.

1.2 *Products.* This document applies to prophylactic and therapeutic products. Prophylactic products are those intended to prevent or control the occurrence of disease, such as vaccines, bacterins, or toxoids. (For simplicity, this document uses the term vaccine instead of prophylactic product.) Therapeutic products are those intended to treat existing conditions, such as antitoxins, hyperimmune serum, or immunostimulants.

1.3 *Efficacy*. Efficacy is the direct effect of a medical intervention on an individual subject. The effect of an intervention program in the population is often termed effectiveness. The notion of effectiveness includes both direct effects and the indirect effects of the intervention at the herd or population level. Herd immunity, which protects nonvaccinated individuals in a group by reducing disease transmission through the vaccinated individuals, is an example of an indirect effect. Vaccine efficacy may be isolated from effectiveness by design or analysis.

1.4 *Design*. The preferred design for animal vaccine efficacy studies is the vaccination-challenge trial. In such studies, each subject receives the same exposure to the virulent pathogen by active challenge. By design, challenge studies aim to isolate the direct effect of the vaccine on the individual subject. Other types of studies, such as those relying on natural exposure, may be considered where warranted.

1.6 *Protocol*. Succeeding sections of this document list important considerations for the materials, methods, and criteria of efficacy studies. Protocols of proposed efficacy studies should address these considerations in addition to those noted in the General Licensing Considerations: Study Practices and Documentation (Veterinary Services Memorandum 800.200).

2. Materials

2.1 *Experimental product*. The applicant is responsible for establishing the validity of the experimental product used to demonstrate efficacy. The experimental product must accurately represent the product

that the firm will produce once a product license is granted. Describe in detail its composition, including antigenic mass. Give its potency and state the potency test method.

2.2 *Preparation of experimental product*. Prepare the experimental product:

2.2.1 In accordance with the filed Outline of Production.

2.2.2 In licensed production facilities. Prepare the experimental product in licensed production facilities in accordance with filed facility documents. If prepared in research facilities, establish that the experimental product fully represents the product that will be prepared in production facilities. Validation of production may be required after scale-up.

2.2.3 At or below minimum potency. The potency of the experimental product should be at or below the minimum potency provided in the Outline of Production for the product.

2.2.3.1 *Live virus vaccines.* For most live virus vaccines, the titer required throughout dating must be at least 0.7 $\log_{10}$ greater than the titer of the product used in the efficacy study.

2.2.3.2 *Live bacterial vaccines*. For most live bacterial vaccines, the bacterial count required throughout dating must be twice that of the product used in the efficacy study.

2.2.3.3 *Inactivated products.* Killed products used in efficacy studies must be at or below the minimum antigen level specified in the Outline of Production.

2.2.4 At the highest passage. Prepare the experimental product at the highest passage from the Master Seed allowed by the Outline of Production. If the experimental product originates in cell culture, prepare it in cells at the highest passage from the Master Cell Stock allowed by the Outline of Production. Generally, the fifth passage from the Master Seed and the twentieth passage from the Master Cell Stock are the highest allowed.

2.3 *Placebo*. State the composition of the placebo or active control treatment.

2.4 *Challenge*. State the nature, composition, and potency of the challenge material.

3. Methods

3.1 *General study design*. Clinical efficacy studies should be prospective, placebo-controlled, randomized, and double-blinded. Vaccine trials should preferably aim to compare product- and placebo- treated subjects by their response to challenge with the virulent pathogen. Immunotherapeutic trials should aim to compare the responses of product- and placebo- treated subjects that have the existing condition. Deviations from these design features should be noted and justified in the protocol.

3.2 *Subjects.*

3.2.1 *Signalment*. Specify the age, breed, sex, source, and other distinguishing features of the subjects. Describe how the subjects represent the target population.

3.2.2 *Enrollment criteria*. List the criteria for enrollment into the study and exclusion of enrolled subjects during the study.

3.2.3 *Identification.* Identify subjects uniquely.

3.2.4 *Environment*. State how the subjects will be grouped, housed, and managed. Give the periods during the study when different treatment groups are in contact or separated. Indicate any incidental treatments or procedures to be done during the study.

3.2.5 *Number of subjects*. Include enough subjects for the study to produce sufficiently precise outcome estimates. Although not required, power calculations based on information from pilot studies and other sources may help in planning the study.

3.3 *Group assignment and treatment allocation*.

3.3.1 *Experimental unit*. Identify the experimental unit. The experimental unit is the individual or smallest group of subjects that may be randomly assigned to a distinct treatment. Indicate any clustering or grouping of units.

3.3.2 *Treatment group assignment.* Describe the randomization structure and method of randomly assigning subjects to treatment groups. Design the study so that randomization takes into account features affecting the independence of observations or the confounding of effects. For example, blocking by subject characteristics such as antibody titer, age, weight, or parity may be important, particularly in studies relying on natural challenge or involving existing conditions. If so, include the blocking plan. Or, if subjects are naturally clustered, indicate whether treatment allocation or sample selection is within or between clusters.

3.3.3 *Group treatment allocation.* Efficacy studies usually include at least one group treated with the experimental product and one treated with an immunologically inert placebo. If, instead of placebo, the control group is to be given an alternative active treatment or left entirely untreated, this should be explained in the protocol. Additional treatment groups may be needed for other treatment regimens or doses. Nonparallel group configurations, such as factorial type designs, should be clearly outlined.

3.3.4 *Group proportions*. Prior information may suggest the proportions for dividing subjects between treated and control groups to optimize the study's efficiency and possibly minimize the total number of subjects. In the absence of such information, equal sized groups may be prudent.

3.4 *Treatment and challenge*.

3.4.1 *Vaccine trials.* Describe the vaccination regimen and challenge method. If the proposed design does not include challenge but relies on natural exposure or previous vaccination, explain the reason for the design.

3.4.2 *Immunotherapeutic trials.* Describe the existing disease condition and treatment regimen.

3.5 *Observations*.

3.5.1 *Observation times.* State the time and frequency of observations.

3.5.2 *Blinding.* Clinical observations should be blinded (masked), so that the observer does not know the subject's status in the study. Laboratory measurements and postmortem examinations should also be blinded. Blinding of observations should include at least the following two levels, or the protocol should justify their absence.

3.5.2.1 *Masked treatment allocation.* The observer does not know which treatment a group has received.

3.5.2.2 *Masked group membership.* The observer does not know the group to which a subject is assigned.

3.6 *Clinical outcomes*.

3.6.1 *Outcome specification.* Define the outcome in accordance with General Licensing Considerations: Study Practices and Documentation, section 2.3.9 (Veterinary Services Memorandum 800.200). The outcome may be specified in terms of a case definition, severity categorization, or natural scale of measurement. Avoid complex scoring schemes that are difficult to analyze and interpret because they incorporate many disparate types of observations. Instead, choose natural scales of measurement or simple grading systems that elicit, rather than conceal, the random nature of the response and clarify, rather than obscure, its clinical meaning.

3.6.2 *Primary outcome.* Specify the primary outcome. Since the conclusion criterion is based on it, the primary outcome should provide the most relevant evidence directly supporting the proposed label claim. Specify a single primary outcome for each claim. If clinically relevant, the primary outcome may be designed as a composite of more than one type of observation or a comparison between more than one summary measure.

3.7 *Data analysis*. Describe the proposed method of analysis and indicate how it is appropriate to the study design and nature of the data.

3.8 *Conclusion criterion*. State the criterion for concluding whether the findings support the proposed claim. Conclusion criteria should be based on the size of estimated treatment effects and their clinical relevance.

3.8.1 *Outcome comparison.* Where appropriate, state the intended comparison of primary outcomes between treatment groups, such as by an estimated difference or ratio. For example, vaccine efficacy is typically assessed by the relative difference known as the prevented fraction.

3.8.2 *Prevented fraction.* The prevented fraction (fractional reduction) is the complement of the risk ratio ($1 - p_2/p_1$, where p_2 is the affected fraction in the treated group and p_1 is the affected fraction in the placebo group).

3.9 *Submit all data.* Submit and summarize all data from the study. Include satisfactory and unsatisfactory results. Submit the results of all studies involving a product associated with a product license application to CVB. This applies, for example, whether or not the results were satisfactory, whether or not the study was repeated, or whether or not it was an exploratory study, such as one designed to select dose or antigen levels.

3.10 *Adverse events.* Record and report all adverse events occurring during the study whether or not they are considered related to vaccination, treatment, or challenge.

3.11 *Laboratory procedures*. Describe procedures for all laboratory analyses.

3.12 *Indirect passive immunization.* For products intended to protect neonates by maternal antibodies from vaccinated dams, studies should be designed according to the proposed vaccination regimen.

3.12.1 If the recommended regimen is to vaccinate the dam for the passive immunization of her offspring, treatment groups should be comprised of adults whose responses are measured by the immunity of their offspring.

3.12.2 If the recommended regimen is to vaccinate both the dam and her offspring for the protection of the offspring, treatment groups should be comprised of adult-neonate units.

3.12.3 If there is more than one recommended vaccination regimen, the efficacy of each recommended regimen must be supported by appropriate treatment groups. Studies of products recommended for both passive and active immunization should include separate groups of passively and actively immunized subjects.

3.13 *Serological outcomes*. Serological responses are not usually sufficient for establishing efficacy. An efficacy claim based on serological data alone will be considered only when there is a substantial scientific basis for accepting that the serological test used is indicative of disease protection.

4. Criteria

4.1 *Label indications.* Data must fully support label indications and accurately reflect the expected performance of the product.

4.2 *Label claims.*

4.2.1 *Prevention of infection.* A claim that it is intended to prevent infection may be made only for products able to prevent all colonization or replication of the challenge organism in vaccinated and challenged animals. If such a conclusion is supported with a very high degree of confidence by convincing data, a label statement such as "for the prevention of infection with [specific microorganism]" may be used.

4.2.2 *Prevention of disease.* A claim that it is intended to prevent disease may be made only for products shown to be highly effective in preventing clinical disease in vaccinated and challenged animals. The entire 95% interval estimate of efficacy must be at least 80%. If so, a label statement such as "for the prevention of disease due to [specific microorganism]" may be used.

4.2.3 *Aid in disease prevention.* A claim that it is intended to aid in disease prevention may be made for products shown to prevent disease in vaccinated and challenged animals by a clinically significant amount which may be less than that required to support a claim of disease prevention (section 4.2.2). If so, a label statement such as "as an aid in the prevention of disease due to [specific microorganism]" may be used.

4.2.4 *Aid in disease control.* A claim that it is intended to aid in disease control may be made for products which have been shown to alleviate disease severity, reduce disease duration, or delay disease onset. If so, a label statement such as "as an aid in the control of disease due to [specific microorganism]" or a similar one stating the product's particular action may be used.

4.2.5 *Other claims.* Products with beneficial effects other than direct disease control, such as the control of infectiousness through the reduction of pathogen shedding, may make such claims if the size of the effect is clinically significant and well supported by the data.

4.3 *Disease form*. When a microorganism is associated with more than one clinical form of disease, limit claims to the disease form(s) for which efficacy has been demonstrated, such as "respiratory form" or "reproductive form." Use specific disease or syndrome names whenever applicable.

4.4 *Administration regimen.* Establish efficacy separately for each route (e.g. intramuscular, subcutaneous, intranasal, in ovo) and regimen (e.g. age and frequency) of administration recommended on the label.

4.5 *Species*. Establish efficacy in each species for which the product is recommended.

4.6 *Age and susceptibility.* Conduct target species immunogenicity studies in fully susceptible animals of the youngest age for which the product is recommended. If, however, interfering levels of maternal antibody may still be present at the youngest recommended age, do one of the following:

4.6.1 Provide data to demonstrate efficacy of the product in the face of expected levels of maternal antibody, or

4.6.2 Indicate on the labeling that the product is for the vaccination of susceptible animals of the minimum age used in the immunogenicity study and recommend revaccination at appropriate intervals until such animals reach an age when interfering levels of maternal antibody would no longer be present.

4.7 *Onset of immunity.* Support with acceptable data any specific claims concerning onset of immunity.

4.8 *Duration of immunity.* Conduct duration of immunity studies to support vaccination recommendations for all new product fractions presented for licensure. Support with acceptable data specific claims for the duration of immunity for any product fraction.